The COVID-19 Treatment Guidelines Panel's Statement on the Emergency Use Authorization of Bamlanivimab for the Treatment of COVID-19

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Bamlanivimab (also known as LY-CoV555 and LY3819253) is a neutralizing monoclonal antibody that targets the receptor-binding domain of the spike protein of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Because this drug may block SARS-CoV-2 entry into host cells, it is being evaluated for the treatment of COVID-19.

On November 9, 2020, the Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) to make bamlanivimab available for the treatment of nonhospitalized patients with mild to moderate COVID-19 who are at high risk for progressing to severe disease and/or hospitalization (see the specific EUA criteria for its use below).[1] The issuance of an EUA does not constitute FDA approval of a product. The COVID-19 Treatment Guidelines Panel (the Panel) reviewed the available evidence from the published data on bamlanivimab for the treatment for COVID-19 and the FDA fact sheet that supported the EUA.

Based on the available evidence, the Panel has determined the following:

- At this time, there are insufficient data to recommend either for or against the use of bamlanivimab for the treatment of outpatients with mild to moderate COVID-19.

- Bamlanivimab **should not be considered** the standard of care for the treatment of patients with COVID-19.

- An interim analysis of the BLAZE-1 study, a Phase 2, randomized, placebo-controlled trial, suggested a potential clinical benefit of bamlanivimab for outpatients with mild to moderate COVID-19. However, the relatively small number of participants and the low number of hospitalizations or emergency department visits make it difficult to draw definitive conclusions about the clinical benefit of bamlanivimab.

- More data are needed to assess the impact of bamlanivimab on the disease course of COVID-19 and to identify those people who are most likely to benefit from the drug. Health care providers are encouraged to discuss participation in bamlanivimab clinical trials with their patients.

- Given the possibility of a limited supply of bamlanivimab, as well as challenges distributing and administering the drug, patients at highest risk for COVID-19 progression should be prioritized for use of the drug through the EUA. In addition, efforts should be made to ensure that communities most affected by COVID-19 have equitable access to bamlanivimab.

- Bamlanivimab should not be withheld from a pregnant individual who has a condition that poses a high risk of progression to severe COVID-19, and the clinician thinks that the potential benefit of the drug outweighs potential risk (see the criteria for EUA use of bamlanivimab below).

- Patients who are hospitalized for COVID-19 **should not receive** bamlanivimab outside of a clinical trial.

- The Panel will continue to evaluate emerging clinical data on the use of bamlanivimab for the treatment of outpatients with mild to moderate COVID-19 and anticipates updating these recommendations as more information becomes available.

Clinical Trial Data

The Blocking Viral Attachment and Cell Entry with SARS-CoV-2 Neutralizing Antibodies (BLAZE-1) trial is a randomized, double-blind, placebo-controlled, Phase 2 trial conducted at 41 centers in the United States to evaluate the safety and efficacy of bamlanivimab for the treatment of mild to moderate COVID-19 in an outpatient setting. Participants received a single intravenous infusion of bamlanivimab within 3 days of having a positive SARS-CoV-2 virologic test result. Participants were excluded if they had a saturation of oxygen (SpO_2) ≤93% on room air, respiratory rate ≥30 breaths/minute, or heart rate ≥125 beats/minute. According to a published interim analysis of the trial, a total of 452 participants were randomized to receive one of three doses of bamlanivimab (700 mg, 2,800 mg, or 7,000 mg) or placebo.[2]

Among the study participants, the median age was 45 years (range: 18–86 years) in the pooled bamlanivimab groups and 46 years (range: 18–77 years) in the placebo group. Although 69.6% (215/309) of the participants in the bamlanivimab groups and 66.4% (95/143) in the placebo group reportedly had risk factors for severe COVID-19, the study population included only a small percentage of participants aged >65 years (10.7% [33/309] in the bamlanivimab groups vs. 14.0% [20/143] in the placebo group). The median time from symptom onset to infusion of bamlanivimab or placebo was 4 days across the groups.

The mean decrease in nasopharyngeal SARS-CoV-2 level from baseline to Day 11 (the primary endpoint) was significantly greater among participants who received the 2,800 mg dose of bamlanivimab than among the placebo-treated participants. The decline in viral load was not significantly different between those who received the 700 mg or 7,000 mg dose of bamlanivimab and those who received placebo.

A prespecified secondary endpoint of COVID-19-related hospitalization, emergency department visit, or death within 28 days of treatment was lower in those who received bamlanivimab than in those who received placebo. However, the percentage of participants in each group who met this endpoint was small (no deaths occurred):

- Placebo: 6.3% (9 of 143)
- All bamlanivimab doses: 1.6% (5 of 309)
  - Bamlanivimab 700 mg: 1.0% (1 of 101)
  - Bamlanivimab 2,800 mg: 1.9% (2 of 107)
  - Bamlanivimab 7,000 mg: 2.0% (2 of 101)

In a post hoc analysis of participants at high-risk for progression to severe COVID-19 (defined as aged ≥65 years or having a body mass index [BMI] ≥35), four of 95 participants (4.2%) in the combined bamlanivimab arms versus seven of 48 (14.6%) participants in the placebo group were hospitalized or had emergency department visits.

In a separate analysis of the BLAZE-1 study reported in the EUA of participants at high risk for hospitalization (using an expanded definition that approximates criteria for those who should be treated with bamlanivimab through the EUA), four of 136 (2.9%) participants in the combined bamlanivimab arms versus seven of 69 (10.1%) participants in the placebo group were hospitalized or had emergency department visits. According to this analysis, the median time to symptom improvement was 6 days for participants who received bamlanivimab and 8 days for those who received placebo.

The safety profile of bamlanivimab at all three doses was reportedly similar to that of the placebo. According to the EUA, among 850 participants in ongoing trials who have received bamlanivimab,

one anaphylaxis reaction and one serious infusion-related reaction have been reported. The bamlanivimab infusions were discontinued, and with treatment, both events were resolved.

A substudy of the A Multicenter, Adaptive, Randomized, Blinded Controlled Trial of the Safety and Efficacy of Investigational Therapeutics for Hospitalized Patients With COVID-19 (ACTIV-3) trial randomized patients hospitalized with COVID-19 to bamlanivimab or placebo, each in addition to remdesivir. On October 26, 2020, enrollment into this bamlanivimab substudy was stopped due to lack of clinical benefit in hospitalized patients.[3]

High-Risk Criteria for Emergency Use Authorization of Bamlanivimab

The FDA EUA allows for the use of bamlanivimab for the treatment of nonhospitalized adults and children aged ≥12 years and weighing ≥40 kg who have a high risk for progressing to severe COVID-19 or hospitalization. High risks specified in the EUA are:

- Individuals aged ≥12 years who have one of the following conditions:
  - BMI ≥35
  - Chronic kidney disease
  - Diabetes mellitus
  - Immunosuppressive disease
  - Currently receiving immunosuppressive treatment
- Individuals aged ≥65 years
- Individuals aged ≥55 years who have:
  - Cardiovascular disease, *or*
  - Hypertension, *or*
  - Chronic obstructive pulmonary disease/other chronic respiratory disease
- Individuals aged 12 to 17 years who have:
  - BMI ≥85th percentile for their age and gender based on the Center for Disease Control and Prevention growth charts; *or*
  - Sickle cell disease; *or*
  - Congenital or acquired heart disease; *or*
  - Neurodevelopmental disorders, for example, cerebral palsy; *or*
  - A medical-related technological dependence, for example, tracheostomy, gastrostomy, or positive pressure ventilation (not related to COVID-19); *or*
  - Asthma or a reactive airway or other chronic respiratory disease that requires daily medication for control.

References

1. Food and Drug Administration. Fact sheet for healthcare providers: emergency use authorization (EUA) of bamlanivimab. 2020. Available at: https://www.fda.gov/media/143603/download. Accessed November 13, 2020.
2. Chen P, Nirula A, Heller B, et al. SARS-CoV-2 neutralizing antibody LY-CoV555 in outpatients with COVID-19. *N Engl J Med*. 2020; Published online ahead of print. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33113295.

3. National Institute of Allergy and Infectious Diseases. Statement—NIH-sponsored ACTIV-3 trial closes LY-CoV555 sub-study. 2020. Available at: https://www.niaid.nih.gov/news-events/statement-nih-sponsored-activ-3-trial-closes-ly-cov555-sub-study. Accessed November 17, 2020.